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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,300	03/23/2001	Timothy W. Synold	1954-336	4635

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EXAMINER
LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/815,300	Applicant(s) SYNOLD ET AL.	
	Examiner David A. Lambertson	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *7,10,12,16-20,24-62,64,66 and 67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9,11,13-15,21-23,63 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 10 is acknowledged.

Claims 7, 10, 12, 16-20, 24-62, 64, 66 and 67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

It is noted that claim 64 was erroneously included in Group I in the original restriction requirement, whereas claim 65 should have been in Group I. Additionally, it is noted that claim 11 should also have been included in Group I. The Office Action reflects that claims 11 and 65 are included in the examination despite their absence in the initial restriction requirement, whereas claim 64 is not examined because the subject matter does not correspond to the elected invention.

Claims 1-6, 8, 9, 11, 13-15, 21-23, 63 and 65 are ready for examination in the instant application. Claims 7, 10, 12, 16-20, 24-62, 64, 66 and 67 are withdrawn.

Priority

Applicant's claim for domestic priority to US Application Nos. 60/191,767 and 60/266,866 under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statements filed August 17, 2001, December 27, 2001 and December 4, 2002 have been considered, and signed and initialed copies are attached to this Office Action.

Drawings

New corrected drawings are required in this application because of the reasons set forth in the attached Draftsperson's review (PTO-948). Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, 9, 11, 13-15, 21-23, 63 and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a method of modifying the pharmacokinetics of a drug by altering the activity of SXR, wherein drug catabolism, intestinal efflux of the drug and biliary excretion of the drug is altered/decreased and oral absorption of the drug and placental xenobiotic exposure of a fetus is altered/increased. Specifically as per the elected invention, an antagonist of SXR is used to decrease its activity. The claims read on a broad genus of methods of altering the activity of SXR (including increasing the activity of SXR using an antagonist) such that drug catabolism, intestinal efflux of the drug and biliary excretion of the drug is altered/increased and oral absorption of the drug and placental xenobiotic exposure of a fetus is altered/decreased (e.g., the opposite activity of what is described when using an antagonist of SXR). Additionally, the use of a broad number of compounds that act as antagonists for SXR is claimed.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics to establish a structure-function relationship for the broad genus.

Applicant claims a method of modifying the pharmacokinetics of a drug by altering the activity of SXR using an antagonist by function only, without any disclosed or known correlation between the elements and their function. While the specification provides teachings that SXR

has an effect on the expression of a number of genes that are involved in the resistance to drugs such as taxanes (the specification focuses primarily on paclitaxel and docetaxel), and that the compound ET-743 acts as an antagonist to SXR in cell culture, the specification does not reasonably describe how to modify the activity of SXR by any method. For example, it is unclear how one would use an antagonist to increase the activity of SXR, a limitation that is commensurate with the genus claim of altering the activity of SXR such that drug catabolism is decreased. This is because the specification clearly teaches that an antagonist (i.e., ET-743) decreases the activity of SXR, the opposite effect of what is included in the claims. Similarly, the specification does not teach a representative number of compounds that are capable of acting as an antagonist to SXR. The instant specification only discloses an individual antagonist (ET-743) that is capable of altering the activity of SXR, and does not describe what the relevant characteristics of ET-743 that would allow the skilled artisan to envision other compounds that would decrease SXR activity. The skilled artisan can only envision a method of using an antagonist to decrease the activity of SXR, specifically the compound ET-743. However, the skilled artisan cannot envision what other compounds would have the property of acting as an antagonist to SXR from this single example, because there is no establishment of a structure-function relationship for ET-743 as it pertains to its antagonistic activities. Similarly, the skilled artisan cannot envision other methods of altering SXR activity that do not involve the use of an antagonist.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the prior art that allows one to envision a representative number of compounds that can alter the activity of SXR (increase or

decrease; specifically decrease as per the specific embodiments of the elected invention) by disclosing structural or functional features of a compound so that one of skill in the art could identify and use said compounds in the instant invention. In fact, with the exception of indicating that paclitaxel has the capacity to increase the activity of SXR in cell culture, the prior art is silent on altering the activity of SXR. Thus the skilled artisan cannot rely on the prior art to see that the applicant was in possession of the claimed genus, both in terms of the method of altering the activity of SXR and in terms of the compounds used to do so.

In conclusion, neither the specification of the instant application or the prior art teaches a structure-function relationship for a representative number of compounds that can be used to alter the activity of SXR, nor do they teach a representative number of methods to perform such activities. The specification only describes using one method, an antagonist, to modulate SXR activity. Furthermore, the specification only discloses a single compound, ET-743, that is an antagonist for SXR without disclosing any structure-function relationship for the compound, and this single compound is not considered a representative number of SXR antagonists. Finally, there is no description of how an antagonist can increase the activity of SXR, which is within the broad claim of altering SXR activity. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claims 1-6, 8, 9, 11, 13-15, 21-23, 63 and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (United States v. Telectronics., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. The nature of the invention is a method of modifying the pharmacokinetics of a drug by administering a compound that alters the activity of SXR, thereby altering the drug metabolism, intestinal efflux, biliary excretion, oral absorption and placental xenobiotic exposure of a fetus for a drug. In the specific elected embodiments, the compound that is administered is an antagonist. Additionally, the claims read on altering the pharmacokinetics of a drug in any circumstance, whereas the specification only provides results concerning the use of cultured cells (for example, as opposed to an organism). The real world use for this invention is a method of reducing the effects of SXR activation on drug metabolism, such as an anti-cancer drug (e.g., a taxane), whereby the reduction increases the efficacy of a treatment procedure, most preferably in a human.

Scope of the invention. The scope of the invention is very broad, claiming the use of virtually any compound in the SXR-altering process, and claiming the ability to modulate the pharmacokinetics of a drug in any system (mammal, single-celled organisms, insect, plant, etc.).

It is important to note that the broad scope of the claims encompasses both increasing and decreasing the activity of SXR by administering an antagonist, which is in and of itself contradictory.

State of the art. Although the claim recites the method as used in any system, the real world use of the invention involves the altering of pharmacokinetics as it pertains to the treatment of patients (e.g., mammals, humans) and the benefits that the alteration of SXR activity would have, for instance, in the administration of anti-cancer agents (as per the specific embodiment where taxane is the drug that is being modulated). The assertion of a real world use in a mammal or human is also supported by the limitations where intestinal efflux, biliary excretion, oral absorption and placental xenobiotic exposure in a fetus are recited, as these limitations inherently indicate the method is used in a multi-cellular organism such as a human. The state of the art is silent regarding the use of compounds to alter the pharmacokinetics of a drug by altering the activity of SXR in a mammal. However, the general state of the art as it concerns the use of cultured cells to predict function in an organism indicates a high degree of unpredictability. Specifically, as it concerns the use of potential anticancer drugs as an example, "many thousands of drugs have shown activity in either cell or animal models, but only 39 are used in chemotherapy," indicating that, "model systems are not predictive at all" (see for example Science **278**: 1041-1042, 1997; specifically page 1041, paragraph #2). In fact, as it regards their correlation to animal models, which are themselves inherently unpredictable, "human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to tumor sites" (see for example Science **278**: 1041-1042, 1997; specifically page 1041, paragraph #3). These statements are relevant to the general nature

of predicting (or not being able to predict) success from a model system (in the instant case, cultured cells) to the desired operating circumstances (an organism). Thus, the state of the art reflects the unpredictability of the invention as claimed in the instant application. As a result, the skilled artisan would be unable to consult the prior art for guidance when practicing the instant invention.

Number of working examples and Guidance provided by applicant. The working examples and guidance provided by the instant specification, in its most specific embodiment, regards the use of a single antagonist to SXR, ET-743. The teachings provided in the specification show the antagonistic activity of ET-743 as it occurs in a cell culture environment, but provides no guidance or examples as to the efficacy or functionality in a mammal or other multi-cellular organism. Furthermore, there is no indication that this compound affects biliary excretion, intestinal efflux, oral absorption or placental xenobiotic exposure of a fetus for a drug, as there is no data reflecting these parameters in an organism. The skilled artisan cannot rely on the instant specification to use the claimed invention because the specification does not teach the skilled artisan how to use any compound commensurate with the scope of the claims. Also, the predictable expectation of antagonizing SXR, thereby altering the pharmacokinetics of a drug for its real world use in a human, is not demonstrated because there is a lack of teachings in a relevant multi-cellular organism.

Level of skill in the art. The level of skill as it regards the instant invention is highly underdeveloped. There is no evidence that the specific compound, ET-743, is effective for the desired purpose of altering the pharmacokinetics of a drug in an organism (its real world use) either in the prior art or in the instant specification. This is amplified as it concerns compounds

for which there are not even cell culture teachings of their effects. Thus, the skilled artisan cannot rely on either the prior art or the instant specification to use the claimed invention as it regards any compound because the specific embodiment has not been demonstrated to operate as claimed.

Unpredictability of the art. The art is highly unpredictable. Applicant has provided evidence that one compound (ET-743) has the ability to act as an antagonist for SXR in a cell culture environment. However, the real world use of the claimed invention is the use of an antagonist against SXR, whereby the compound is effective to alter the pharmacokinetics of a drug in a mammal (e.g., a human) so as to increase the efficacy of the treatment of the organism. Furthermore, there is no evidence that intestinal efflux, biliary excretion, oral absorption or placental xenobiotic exposure of a fetus is altered in any way because there is no *in vivo* data to show this occurs. As a result, the skilled artisan would be required to practice undue trial and error experimentation to use the claimed invention for its real world purpose.

Amount of experimentation required. A great deal of unpredictable and undue trial and error experimentation is required in order to make and use the claimed invention. The skilled artisan would be required to test the system in a mammal in order to see if it actually worksfor the specific example. In addition, the skilled artisan would be required to test a variety of different compounds for which there are not even teachings in cell culture concerning their ability to antagonize SXR, in the same manner in order to make and use the claimed invention.

In conclusion, the test of enablement involves many factors, the most relevant of which are discussed above. The discussion outlines that the invention is a method of modifying the pharmacokinetics of a drug by altering SXR activity, where the real world use is for treating

mammals undergoing drug therapies. The most specific embodiment has not been demonstrated to be an effective compound for its real world use in an organism; rather it has only been demonstrated to be effective in cell culture. Furthermore, in the absence of data concerning an organism, it is impossible to predict that intestinal efflux, biliary excretion, oral absorption of a drug or placental xenobiotic exposure of a fetus would be altered. As per the state of the art, cell culture is not a predictive model for function in an organism, therefore unpredictable and undue trial and error experimentation would be required to make and use the claimed invention. The scope of the claims is very broad, encompassing any compound, wherein only a single compound has been taught in the instant specification and the prior art. Therefore, it is clear that the specification in view of the prior art has not enabled the skilled artisan to make and use the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8, 11, 14 and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 8, 11, 14

and 21 of copending Application No. 09/905,989 (a.k.a. US 2002/0061836; henceforth the '989 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant invention are genus claims that encompass the specific claims of the '989 application. Because the genus claims of the instant claims (wherein modification of drug pharmacokinetics under any circumstances) encompass the specific claims of the '989 patent (wherein the modification of drug pharmacokinetics occurs specifically within a mammal), the specific claims anticipate the genus claims.

It is important to note that this rejection concerns the generic claims that are common between the two applications, and does not reflect the specific embodiments (i.e., the use of an agonist versus an antagonist, or the increase in drug metabolism versus a decrease in drug metabolism).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
April 7, 2003

PATENT EXAMINER
Gerald G. Letters Jr
A.U. 1636